


# Cryoglobulinemia and double-filtration plasmapheresis: Personal experience and literature review

Hamza Naciri Bennani<sup>1</sup> | Augustin Twite Banza<sup>1</sup> | Florian Terrec<sup>1</sup> |  
Johan Noble<sup>1,2</sup> | Thomas Jouve<sup>1,2</sup> | Lionel Motte<sup>1</sup> | Paolo Malvezzi<sup>1</sup> |  
Lionel Rostaing<sup>1,2,3</sup> 

<sup>1</sup>Department of Nephrology,  
Hemodialysis, Apheresis, and Kidney  
Transplantation, Grenoble University  
Hospital, Grenoble, France

<sup>2</sup>Grenoble Alpes University, Grenoble,  
France

<sup>3</sup>Ramathibodi Hospital, Mahidol  
University, Bangkok, Thailand

## Correspondence

Lionel Rostaing, Service de Néphrologie,  
Hémodialyse, Aphèreses et  
Transplantation Rénale, CHU Grenoble-  
Alpes, Avenue Maquis du Grésivaudan,  
38700 La Tronche, France.  
Email: [lrostaing@chu-grenoble.fr](mailto:lrostaing@chu-grenoble.fr)

## Abstract

**Background:** Cryoglobulinemia is defined as the presence of an abnormal immunoglobulin that may be responsible for vasculitis of small-caliber vessels. Apheresis can be used in order to temporarily eliminate circulating cryoglobulins. The aim of this study was to assess the effectiveness of apheresis (double-filtration plasmapheresis-DFPP-) in symptomatic and/or severe cryoglobulinemias.

**Methods:** Four male patients presenting cryoglobulinemic vasculitis and who received DFPP sessions were included.

**Results:** Their mean age was  $57 \pm 15$  years. One patient had hepatitis-C virus (HCV)-related cryoglobulinemia and the other three patients were carriers of an IgM Kappa monoclonal gammopathy. Mean duration of follow-up was  $15 \pm 2$  months. DFPP allowed healing of ulcerative skin lesions in the first patient and remission of nephrotic syndrome in the other patients after a median of 6(5–10) sessions.

**Conclusion:** DFPP can be used safely in cryoglobulinemic-vasculitis and can be considered early to achieve a faster and sustained clinical-biological response.

## KEYWORDS

chronic hepatitis C, cryoglobulinemia, double-filtration plasmapheresis, membranoproliferative glomerulonephritis, rituximab, Waldenström disease

## 1 | INTRODUCTION

Cryoglobulinemia is defined as the persistent presence in serum of abnormal immunoglobulins (Ig) that precipitate

at low temperatures and dissolve again upon warming [1]. Cryoglobulins may be composed of only a monoclonal Ig (type I cryoglobulinemia), of a monoclonal Ig bound to the constant domain of polyclonal Ig heavy chains (mixed type II cryoglobulinemia), or of only polyclonal Ig (mixed type III cryoglobulinemia) [1]. The disease mainly involves small to medium-sized blood vessels

Hamza Naciri Bennani and Augustin Twite Banza have contributed equally to this study.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Therapeutic Apheresis and Dialysis* published by John Wiley & Sons Australia, Ltd on behalf of International Society for Apheresis and Japanese Society for Apheresis.

and causes vasculitis due to cryoglobulin-containing immune complexes. This generally leads to a systemic inflammatory syndrome characterized by fatigue, arthralgia, purpura, neuropathy, and glomerulonephritis [2].

Wintrobe and Buell, in 1933, were the first to describe cryoglobulinemia in a patient with multiple myeloma: they made the observation that when his serum was cooled this resulted in an unusual precipitate that disappeared subsequently upon heating [3]. He presented with Raynaud phenomenon, distal acrocyanosis, epistaxis, and retinal thrombosis. However, the term “cryoglobulin” was coined later to describe the phenomenon of cold-precipitable serum Ig [4].

Hepatitis C virus was discovered in 1989 [5], and it was soon shown that most cases of non-hematological-related cryoglobulinemia were indeed related to chronic HCV infection [6].

In 1960 therapeutic apheresis was given to a patient that presented with Waldenström macroglobulinemia [7]. Since then, apheresis has undergone huge developments. In their 2019 recommendations, the American Society of Apheresis classified severe/symptomatic cryoglobulinemia as category II, that is, a category where apheresis is accepted as a second-line therapy using either plasmapheresis (grade 2A) or immunoadsorption (grade 2B) [8].

## 2 | PATIENTS AND METHODS

### 2.1 | Study population

This retrospective single-center study was conducted in a French university hospital between January 1, 2019 and December 31, 2020. All patients had presented with cryoglobulinemia-related vasculitis and received DFPP as part of their therapy. For all patients, DFPP was in association with immunosuppressive drugs.

Complete remission was defined as an absence of any disease activity attributable to vasculitis. Partial remission was defined by a  $\geq 50\%$  decrease in disease activity score (BVAS) in the absence of a new vasculitis-related manifestation. Relapse was defined as re-occurrence of vasculitis-related clinical and/or biological manifestations. Refractory cases were defined according to EULAR guidelines ([https://www.eular.org/recommendations\\_eular\\_acr.cfm](https://www.eular.org/recommendations_eular_acr.cfm)), which are defined as follows:

- an active and progressive disease where conventional therapy has been implemented at least 4 weeks ago;
- no response as defined by a decrease in Birmingham Vasculitis Activity Score (BVAS)  $\leq 50\%$  after 6 weeks of conventional therapy;

- a persisting chronic disease defined by the presence of at least one major symptom/parameter or three minor symptoms/parameters from the vasculitis-activity score items, for example, BVAS or BVAS/Wegener's Granulomatosis (BVAS/WG), after at least 12 weeks of conventional therapy.

### 2.2 | Double-filtration apheresis

DFPP was performed using a Plasauto  $\Sigma$  machine (Asahi Kasei Medical, Tokyo, Japan). The patients' plasma was separated from blood cells using a first filter (Plasmaflo OP-08 W), then it was treated using a second filter (either Cascadeflo EC-30 W, Cascadeflo EC-20 W or Cascadeflo EC-50 W) depending on molecular weight of the substance to be eliminated. Patients 1, 2, and 4 used Cascadeflo EC-50 in order to eliminate IgM. While patient 3 used Cascadeflo EC-30 W on the first session then Cascadeflo EC-20 W on the subsequent sessions so that IgG would be eliminated. The volume of plasma treated was equal to 1.5 times the plasma volume, calculated using the Kaplan formula:  $PV = 0.065 \times \text{weight (kg)} \times (1 - \text{hematocrit})$  [9]. Blood flow was 150 ml/min and plasma separation was  $\sim 25\%$  of maximum blood-flow rate. During DFPP,  $<500$  ml of 4% albumin are needed to be infused per session, which corresponds to plasma rejection, that is, 5–10% of plasma volume treated. Extracorporeal anticoagulation was based on regional anticoagulation using citrate with reinjection of calcium into the venous return line according to ionized calcium, which was maintained at 1.15–1.35 mmol/L. Vascular access required the insertion of a central venous jugular or femoral catheter, which was removed at the end of apheresis therapy.

### 2.3 | Collected data and statistical analyses

Clinical and biological data were collected from electronical medical files (CristalNet software). Apheresis data were collected through the paper records of each session. Data were computerized on Excel 2016 software. Quantitative variables were expressed as mean  $\pm$  SD.

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by CNIL (French National committee for data protection; approval number 1987785v0). The biobank collection number is BRIF BB-0033-00069. Informed consent was obtained from all subjects involved in the study.

### 3 | RESULTS

During the study period, we had four male patients presenting with cryoglobulinemic vasculitis and for whom apheresis was part of the therapy. Their mean age at the time of diagnosis was  $57 \pm 15$  years. Table 1 summarizes the characteristics of the four patients that received double-filtration plasmapheresis.

#### 3.1 | Case descriptions

Case n°1 was a 62-year-old male that had received chronic hemodialysis for 17 years. End-stage kidney disease (ESKD) was consecutive to type I cryoglobulinemia (IgM kappa)-related membranoproliferative glomerulonephritis (MPGN). In cold weather he sometimes experienced cutaneous ulcerations (on his toes), which were treated by rituximab ( $375 \text{ mg/m}^2$ ).

In October 2019, he presented with persisting very painful bilateral plantar ulcerations without any other associated symptoms/sign. There was no osteitis. Biological tests showed hypocomplementemia, a decrease in IgG levels ( $4.9 \text{ g/L}$ ), and an increase in IgM levels ( $4.6 \text{ g/L}$ ). Cryoprecipitate was  $30 \text{ mg/L}$  and was mostly composed of monoclonal IgM kappa. At that point we decided to implement 10 DFPP sessions (three per week for 2 weeks, then two per week for 2 weeks). After the third and sixth sessions he was infused with  $375 \text{ mg/m}^2$  of rituximab. At 8 days after starting this therapy, the pain had disappeared, and the ulcerations began to heal. By the end of therapy, the ulcerations were no longer present; IgM had decreased to  $1.02 \text{ g/L}$  and cryoprecipitate to  $6 \text{ mg/L}$ . By 16 months later, the patient was still in remission with no detectable cryoprecipitate.

Case n°2 was a male patient aged 83 years. He had been diagnosed 10 years previously with type II IgM kappa cryoglobulinemia-related membranoproliferative glomerulonephritis. This was within the setting of non-Hodgkin lymphoma. At that time, he received rituximab at  $375 \text{ mg/m}^2$  per week for up to four injections: this resulted in long-lasting remission until 2017 when he suffered a relapse of lymphoma. He therefore received another four weekly rituximab infusions ( $375 \text{ mg/m}^2$ ). Remission then lasted from August 2017 to November 2029. At that point he presented with diffuse edema and nephritic syndrome. Biological examinations found acute renal failure, that is, serum creatinine had increased from  $220 \mu\text{mol/L}$  (estimated glomerular-filtration rate [eGFR] was  $21 \text{ ml/min}$ ) to  $307 \mu\text{mol/L}$  (eGFR was  $16 \text{ ml/min}$ ), associated with gross hematuria and proteinuria of  $2.36 \text{ g/day}$ . In addition, there was an increase in IgM level to  $3.22 \text{ g/L}$  (and a decrease in IgG and IgA levels) as well

as hypocomplementemia. Cryoprecipitate was  $300 \text{ mg/L}$  (mostly composed of monoclonal IgM kappa). A kidney biopsy was declined by the patient. We implemented a combined therapy comprising five DFPP sessions (three the first week and two the second week) combined with four weekly rituximab ( $375 \text{ mg/m}^2$ ) infusions: the first was started after the third DFPP session. By day 14 after starting the combined therapy there was a huge improvement, that is, IgM levels decreased to  $1.85 \text{ g/L}$ , renal function returned to baseline (serum creatinine of  $200 \mu\text{mol/L}$ , eGFR of  $24 \text{ ml/min}$ ) proteinuria decreased to  $1 \text{ g/day}$ , and cryoprecipitate was  $50 \text{ mg/L}$ . By 15 months later, he was still in remission, that is, serum creatinine of  $189 \mu\text{mol/L}$  (eGFR of  $28 \text{ ml/min}$ ), proteinuria of  $422 \text{ mg/g}$ , with no microscopic hematuria. Cryoprecipitate was negative.

Case n°3 was a 54-year-old male that had been diagnosed in December 2019 with hepatitis C virus-related asymptomatic cirrhosis. He was referred to our department in March 2020 because he presented with cryoglobulinemia type III-related membranoproliferative glomerulonephritis. He had diffuse edema, nephrotic-range proteinuria ( $5 \text{ g/day}$ , hypoalbuminemia at  $23 \text{ g/L}$ ) and acute renal failure (serum creatinine was  $250 \mu\text{mol/L}$ , eGFR was  $24 \text{ ml/min}$ ). In addition, he had hypocomplementemia, polyclonal hypergammaglobulinemia; cryoprecipitate was  $100 \text{ mg/L}$  (polyclonal IgG). He was given hemodiafiltration in addition to daily DFPP session (up to five); after the first three DFPP sessions methylprednisone (MP)  $10 \text{ mg/kg}$  was infused; MP was followed by oral prednisone, with the dose slowly tapered. Rituximab was infused at  $1 \text{ g}$  after the fifth DFPP session and at 2 weeks later. Finally, anti-HCV treatment was implemented (glecaprevir  $300 \text{ mg/day}$  plus pibrentasvir  $120 \text{ mg/day}$ ) for 8 weeks. Two weeks after starting DFPP (and steroids) IgG had decreased from  $8.8$  to  $3.1 \text{ g/L}$ , renal function was markedly improved (serum creatinine was  $123 \mu\text{mol/L}$ , eGFR was  $54 \text{ ml/min}$ ), albuminemia level was increased to  $32 \text{ g/L}$ , proteinuria was decreased to  $1.5 \text{ g/day}$ , cryoprecipitate was negative, and complement factors were normalized. By 18 months later, he was still in complete remission with good renal function, that is, serum creatinine was  $107 \mu\text{mol/L}$  (eGFR was  $67 \text{ ml/min}$ ).

Case n°4 was a male patient aged 72 years. Eight years previously he had been diagnosed with Waldenström disease associated with cryoglobulinemia type I-related membranoproliferative glomerulonephritis. He received six cycles of R-CHOP chemotherapy (comprising rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). He improved to remission; his baseline renal function was defined by serum creatinine of  $95 \mu\text{mol/L}$  (eGFR of  $69 \text{ ml/min}$ ); proteinuria was

TABLE 1 Characteristics of the four patients that received double-filtration plasmapheresis (DFPP)

Protocol									Follow-up duration (months)	Outcomes	
Age	Apheresis		Drugs	Type of cryoglobulinemia	Etiology	Clinical manifestations	Kidney biopsy	Biology at diagnosis			
Patient	Gender	(years)									
1	M	62	DFPP (10 sessions in 4 weeks)	Rituximab	I	IgM Kappa	Bilateral plantar ulcerations	MPGN	IgG = 4.9 g/L, IgM = 4.6 g/L, Cryocrit = 30 mg/L	16	Skin healing IgM = 1.02 g/L, Cryocrit = 6 mg/L
2	M	83	DFPP (5 sessions in 2 weeks)	Rituximab	II	IgM Kappa (non-Hodgkin lymphoma)	Nephrotic syndrome, acute kidney injury	MPGN	Pu = 2.3 g/day, Creatinine = 307 μmol/L, eGFR = 16 mL/min, IgM = 3.22 g/L, cryocrit = 300 mg/L	15	Pu = 0.4 g/day, Creatinine = 189 μmol/L, eGFR = 28 ml/min, IgM = 1.85 g/L, cryocrit negative
3	M	54	DFPP (5 sessions in 1 week)	Steroids, Rituximab, Glecaprevir, Pibentasvir	III	HCV	Nephrotic syndrome, acute kidney injury	MPGN	Pu = 5 g/day, Creatinine = 250 μmol/L, eGFR = 24 ml/min, cryocrit = 100 mg/L Albumin = 23 g/L	18	Pu = 1.5 g/day, Creatinine = 107 μmol/L, eGFR = 67 ml/min, cryocrit negative, Albumin = 32 g/L
4	M	72	DFPP (5 sessions in 2 weeks)	Rituximab, cyclophosphamide, Dexamethasone	I	Waldenström disease (IgM kappa)	Nephrotic syndrome, acute kidney injury	MPGN	Pu = 1.5 g/day, Creatinine = 224 μmol/L, eGFR = 24 ml/min, IgM = 5.6 g/L, cryocrit = 10 mg/L	1	Pu = 0.5 g/day, Creatinine = 92 μmol/L, eGFR = 80 ml/min, IgM = 2.5 g/L, cryocrit negative
4	M	72	DFPP (3 sessions in 1 week)	Bortezomib, dexamethasone then rituximab	I	Waldenström disease (IgM kappa)	Nephrotic syndrome, acute kidney injury	MPGN	Pu = 3.3 g/day, Creatinine = 135 μmol/L, eGFR = 46 ml/min, IgM = 8 g/L, cryocrit = 25 mg/L	12	Pu = 0.2 g/day, Creatinine = 138 μmol/L, eGFR = 42 ml/min, cryocrit negative



negligible at 0.3 g/g of creatininuria. In October 2019 he presented with a renal relapse of cryoglobulinemic vasculitis, that is, he had diffuse edema, proteinuria was 1.5 g/g of creatininuria, acute renal failure (serum creatinine rose to 224  $\mu\text{mol/L}$  (eGFR was 24 ml/min), IgM was 5.6 g/L, and cryoprecipitate was 10 mg/L (mostly monoclonal IgM kappa). A renal biopsy showed evidence of membranoproliferative glomerulonephritis with diffuse microthrombi. We therefore started five sessions of DFPP (every other day) plus chemotherapy (rituximab—cyclophosphamide—dexamethasone). He progressively improved; by 3 months later, renal function had recovered (serum creatinine was 92  $\mu\text{mol/L}$ , eGFR was 80 ml/min, proteinuria was 0.5 g/g of creatininuria, IgM level had decreased to 2.5 g/L, and cryoprecipitate was negative. However, a month later (February 2020) he had a renal relapse, that is, diffuse edema, nephrotic-range proteinuria (3.3 g/g of creatininuria plus hypoalbuminemia of 23 g/L), and acute renal failure (serum creatinine was 135  $\mu\text{mol/L}$ , eGFR was 46 ml/min). IgM levels had increased to 8 g/L and cryoprecipitate was 25 mg/L (monoclonal IgM). At that point, he received three sessions of DFPP followed by third-line chemotherapy consisting of dexamethasone plus bortezomib. At 1 month later (March) he had mildly improved, that is, it was only partial remission because, even though serum creatinine was stable at 131  $\mu\text{mol/L}$  (eGFR was 50 ml/min) and edema was absent, albuminemia had increased to 35 g/L, proteinuria had decreased to 1.24 g/g of creatininuria as had IgM (5 g/L), and cryoprecipitate was negative. In May 2020 he had a relapse of overt nephrotic syndrome without an increase in serum creatinine; complement factors (C3 and CH50) were low. Cryoprecipitate was negative. He was placed on rituximab as a monotherapy (375 mg/m<sup>2</sup> once a week for 4 weeks, and then every 2 months). In December 2020, renal function had become stable (serum creatinine was 138  $\mu\text{mol/L}$ , eGFR at DFG was 42 ml/min), proteinuria was low at 100 mg/g of creatininuria, and cryoprecipitate was negative. In January 2022, renal function was stable (serum creatinine was 135  $\mu\text{mol/L}$ , eGFR at DFG was 45 ml/min), and proteinuria was almost negative (0.18 g/g of creatininuria).

## 4 | DISCUSSION

In these case reports, we describe patients that had cryoglobulinemia-related vasculitis. The DDPP given at the very beginning of a specific therapy probably helped in inducing rapid remission.

Cryoglobulinemias are encountered (mostly) in two settings: chronic hepatitis C virus infection (type II cryoglobulinemia) and monoclonal gammopathies, such as IgM (type I cryoglobulinemia). When the cryoprecipitate

concentration is (very) high this can result in vasculitis manifestations involving the skin, the kidneys, the central nervous system, the heart, etc. Indeed, as this systemic disease can be life-threatening it requires specific therapies that can be efficacious within very short time frames. However, such therapies for type I cryoglobulinemia are based on high doses of IV steroids and/or rituximab and/or chemotherapy, and treatment with antiviral agents for type II HCV infections, and these approaches are not immediately effective. Thus, the use of apheresis techniques, given soon after diagnosis, can act as a bridge to quickly and efficiently remove cryoglobulins as a first-line therapy. Indeed, it has been already shown, in the setting of cryoglobulinemia-related vasculitis that is unresponsive to pharmacological therapies, that apheresis can be an interesting option (Table 2).

Before the era of direct-acting antivirals (DAA), cryoglobulinemia was associated with HCV infection in 70–90% of cases [28]. Symptomatic cryoglobulinemia vasculitis (CV) can occur in 5–10% of patients with HCV-associated cryoglobulinemia. The most frequent manifestations are cutaneous, with recurrent purpura, articular with joint pains, neurologic with peripheral neuropathy, and renal with membranoproliferative glomerulonephritis. The advent of DAAs against hepatitis C virus has dramatically changed the management of chronic HCV infection. Patients with HCV—cryoglobulinemia vasculitis have high rates of sustained virological response (74–100%) and complete or partial clinical remission (61–100%) after treatment with DAAs [28].

Therapeutic apheresis (TA) is generally used in cases of severe renal impairment, skin necrosis, intestinal ischemia, cardiac, and/or central nervous-system vasculitis. However, no randomized controlled study on the use of apheresis is available on this subject in the literature, but several series and case reports have been published.

Marson et al. [18], in a multicenter retrospective study that included 159 patients with cryoglobulinemia, including 113 HCV-positive patients, showed that the efficacy of TA, used in 70% of patients with a median number of 10 sessions (5–26), was judged to be very good (complete remission) in 12% of cases, good (partial remission) in 38% of cases, transient in 25% of cases, and insufficient in 22% of cases. Patients with hyper-viscosity showed a very good response. Non-response to TA was observed mainly in the event of multi-visceral failure. The survival of patients with a very good, good, or transient response to TA was better than that of non-responders ( $p < 0.0001$ ) [18].

A series, evaluated by Ferri et al. [14], evaluated the management of renal impairment by prolonged plasma-exchange sessions: nine patients presented with mixed cryoglobulinemia with renal impairment (such as severe



TABLE 2 Studies evaluating apheresis in cryoglobulinemia

References	Types of studies	Number of patients	Sex	Age (years)	Protocol		Type of cryoglobulinemia	Etiology	Clinical manifestations	Kidney biopsy	Biology at diagnosis	Follow-up duration (months)	Outcomes
					Apheresis	Drugs							
Okuyama [10]	R	1	M	66	DFPP (5 sessions in 2 weeks)	PEG-interferon + Ribavirin	II	HCV	Nephrotic syndrome, acute kidney injury	MPGN	Pu = 9 g/day, eGFR = 59 ml/min, IgG = 19.4 g/L, IgM = 1.07 g/L, IgA = 2.45 g/L	18	Pu = 6 g/day, eGFR = 59 ml/min
Muro [11]	R	1	M	68	Cryofiltration (5 sessions) + PE (3 sessions)	Steroids + glecaprevir-pibrentasvir + rituximab	II	HCV	Nephrotic syndrome, acute kidney injury	MPGN	Pu = 7.4 g/day, Creatinine = 185 μmol/L, Albumin = 41 g/L, IgM = 4.79 g/L, C3 = 23 g/L, IgG = 6.92 g/L, C3 = 56 mg/dl, C4 = 2.8 mg/dl, cryocrit 4%	27	Pu = 0.3 g/g, Creatinine = 140 μmol/L, Albumin = 41 g/L, IgM = 4.79 g/L, C3 = 67 mg/dl, C4 = 2.8 mg/dl, cryocrit 4%
Taniyama [12]	R	4	M	57 ± 15	Cryofiltration (4 sessions in 3 cases and 1 session in 1 case)	Steroids ± PEG-interferon ± Ribavirin	II	HCV in 3 cases	Purpura, nephrotic syndrome, acute kidney injury or/peripheral neuropathy	MPGN	Pu = 4.9 ± 0.7 g/day, Creatinine = 145 ± 31 μmol/L, Albumin = 25 ± 3 g/L	3	Pu = 0.5 ± 0.5 g/day, Creatinine = 95 ± 29 μmol/L, Albumin = 39 ± 0.5 g/L
Siami [13]	R	1	M	44	PE (15 sessions) then cryofiltration (18 sessions)	Steroids + PEG-interferon + CYP + CysA	II	HCV	Skin ulcerations		Cryoglobulin = 6157 μg/mL, Albumin = 22 g/L	1	Skin healing Cryoglobulin = 420 μg/mL, Albumin = 24 g/L
Ferri [14]	P	9	5 M + 4 F	48 ± 11	PE in all patients (3 sessions per week for 2 weeks then 2 sessions per week for 2 weeks then according to clinical response)	Methylprednisolone in 4 patients	II	Primitive	Nephrotic syndrome, purpura, arthralgias	MPGN	Pu = 5.2 ± 5.0 g/day, Creatinine = 299 ± 193 μmol/L, IgG = 6.06 ± 3.3 g/L, IgM = 1.55 ± 0.88 g/L, CH50 = 61 ± 59 U/mL, cryocrit 4.5 ± 4.2%	1	Pu = 2.1 ± 1.6 g/day, Creatinine = 158 ± 79 μmol/L, IgG = 3.93 ± 2.47 g/L, IgM = 0.92 ± 0.44 g/L, CH50 = 62 ± 57 U/mL, cryocrit 0.9 ± 0.8%
Reik [15]	R	1	M	51	PE (5 sessions)	Steroids + Cyclophosphamide	II	Primitive	Skin ulceration, Encephalopathy, Nephritis	MPGN	Pu = 0.62 g/day, Creatinine = 96 μmol/L, eGFR = 47 ml/min, Albumin = 21 g/L, IgM = 6.92 g/L, C4 = 12 mg/dl, cryocrit 12.5%	1	Mental statut normal, cryocrit 3%
Kiyomoto [16]	R	1	F	69	Cryofiltration	Steroids + PEG-interferon	II	HCV	Nephrotic syndrome, arthralgias	MPGN	Pu = 4.4 g/day, eGFR = 19 ml/min, Albumin = 21 g/L, IgM = 3.64 g/L, CH50 = 23 U/mL	1	Pu = 1.2 g/day, eGFR = 33.7 ml/min, IgM = 1.01 g/L, CH50 = 23 U/mL
Sinha [17]	R	2	F	79 and 66	Cryofiltration (5 sessions)	Steroids + Cyclophosphamide	I, II	Primitive	Skin ulceration, Nephrotic syndrome	MPGN	Pu = 13 g/g and 3.8 g/g, Creatinine = 220 and 150 μmol/L	NS	Pu = 0.6 g/g and 1.1 g/g, Creatinine = 146 μmol/L and 111 μmol/L
Marson [18]	R	159	117 F + 42 M	68–74]	PE (70.4%), DFPP (23.9%) and DFPP + PE (5.7%) = median was 10 sessions per patient The overall duration of AT was<1 year in 89 cases (56.0%), 1–2 years in 26 (16.3%), and >2 years in 44 (27.7%); six patients	Steroids (86.8%), Cyclophosphamide (100%), rituximab (30.2%),Colchicine (14.5%), PEG-interferon + ribavirin (19.5%), Entecavir in one patient	II in 105 cases	HCV in 113 cases, HBV in 1 case	Peripheral neuropathy (54.7%), cutaneous vasculitis (47.8%), CKD in 43 cases, multi-organ damage (8.8%), Hyperviscosity syndrome (2.5%)	MPGN in 29 cases	NA	48	The overall response to treatment after the last AT session was rated very good in 19 cases (11.9%), good in 64 (37.7%), partial/transient in 40 (25.2%), and insufficient/unevaluable in 36 (22.6%). 59 patients died. The probability of dying was five times higher in our



TABLE 2 (Continued)

References	Types of studies	Number of patients	Sex	Age (years)	Protocol		Type of cryoglobulinemia	Etiology	Clinical manifestations	Kidney biopsy	Biology at diagnosis	Follow-up duration (months)	Outcomes
					Apheresis	Drugs							
Yang [19]	R	1	F	50	PE (5 sessions then 4 times per week for 3 weeks)	Rituximab then thalidomide + dexamethasone then mycophenolate mofetil	I (IgM $\kappa$ monoclonal)	plasma cell dyscrasia	bilateral lower extremity ulcers, acute angle-closure glaucoma	NA	NA	8	patients who did not respond to AT, and the risk of death due to CV-related causes was 11 times higher.
Ramunni [20]	R	1	M	39	DFPP (30 sessions in 6 months)	PEG-interferon + ribavirin + steroids then rituximab	I	HCV	perimalleolar ulcers with severe acute pain associated with bilateral cyanosis of the fourth toes, functional impotence, and difficulties in walking.	NA	Fibrinogen = $2.8 \pm 0.4$ g/L, IgM = $3.8 \pm 0.8$ g/L, C4 = $7.1$ mg/dl, cryocrit 15%	6	Three months after her last plasmapheresis session, the patient's ulcers had resolved with scarring and atrophy on her legs.
Stefanutti [21]	P	17	14 F + 3 M	63.5 (43–79)	Immunoadsorption (9 patients for 12 weeks)	PEG-interferon + ribavirin + steroids, cyclophosphamide, cyclosporine, melphalan	II	HCV	peripheral neuropathy, Sjogren syndrome, rash, nephritis, lower extremity vasculitis, skin ulcer with/without necrosis	NA	NA	6	Significant higher percentage of remission of three severe clinical complications occurred in the group with IA ( $P = 0.05$ ); lower limb ulcer, lower limb vasculitis, skin ulcer with necrosis
Olson [22]	R	1	M	80	PE (17 sessions)	R-Bendamustine then carfilzomib, dexamethasone + rituximab	I	Waldenström macroglobulinemia	ulcerating skin lesions in his bilateral lower extremities	NA	cryocrit 33%, IgM = $4.46$ g/L	3	cryocrit 5%, Skin lesions have fully healed
Delaney [23]	R	1	F	81	PE (13 sessions)	NA	II	Primitive	Nephritis, leg ulcers with necrosis, purpura	MGPN	Pu = $2.32$ g/day, eGFR = $28$ ml/min, Albumin = $32$ g/L, IgM = $4.08$ g/L, cryocrit 3%	28 3	Pu = $0.11$ g/day, eGFR = $28$ ml/min, cryocrit $0.5\%$ Purpura disappeared, leg ulcers healed
Braun [24]	R	1	F	78	PE (59 sessions)	Steroids + Cyclophosphamide then rituximab	II	Primitive	peripheral neuropathy, neurogenic muscular atrophy, skin ulcers, arthritis and immune complex glomerulonephritis.	MGPN	Pu = $0.12$ g/day, creatinine = $116$ $\mu$ mol/L, cryocrit 10%	21	Cryocrite $<2\%$ Remission of clinical symptoms Patient is able to walk with assistance.
Stefanutti [25]	R	4	F	$63 \pm 4$	Immunoadsorption (6 sessions per patient)	NA	II	HCV	peripheral neuropathy, Sjogren syndrome, rash, myositis, lower extremity vasculitis	NA	NA	1	Reduce the cryocrit from 23% to 83% Peripheral neuropathy was improved in 2 patients Lower extremity vasculitis was improved in 2 patients

(Continues)

TABLE 2 (Continued)

References	Types of studies	Number of patients	Sex	Age (years)	Protocol	Drugs	Type of cryoglobulinemia	Etiology	Clinical manifestations	Kidney biopsy	Biology at diagnosis	Follow-up duration (months)	Outcomes
Scarpato [26]	R	7	NA	NA	PE (1 session every 15 days)	NA	II	HCV	neuropathies refractory: 4 patients with motory neuropathy, 3 with sensory neuropathy	NA	NA	6	full remission of the motor disturbances and 80% remission of sensory disturbances in one patient and total remission in two
Namba [27]	R	1	M	67	DFPP (5 sessions)	Interferon-alpha then PEG-interferon + ribavirin	II	HCV	Nephrotic syndrome	MGPn	Pu = 5.5 g/g, eGFR = 50 ml/min, Albumin = 28 g/L, IgM = 3.6 g/L, IgG = 11.7 g/L	1	Pu = 0.4 g/g, eGFR = 70 ml/min

MPGN) and received plasma exchange alone or in association with corticosteroids, without cytotoxic agents. Five patients improved 3 weeks after starting plasma exchange, and no clinical relapse occurred when sessions were reduced or interrupted: that is, serum creatinine was  $299 \pm 193$  vs.  $158 \pm 79$   $\mu\text{mol/L}$  before, proteinuria was  $5.2 \pm 5.0$  vs.  $2.1 \pm 1.6$  g/day before, and cryocrit was  $4.5 \pm 4.2\%$  vs.  $0.9 \pm 0.8\%$  before.

In our series, the patient that had type III mixed cryoglobulinemic vasculitis secondary to HCV presented with MPGN, resulting in nephrotic syndrome and severe renal failure. He had received DFPP (five sessions) combined with rituximab (1 g on D0 and D15), corticosteroids, and anti-HCV treatment. By the 12th day of treatment, there was regression of edema associated with improved renal function (plasma creatinine at 123 vs. 250  $\mu\text{mol/L}$ ), a decrease in proteinuria (1.5 vs. 5 g/day), normalization of serum complement, and negative cryoglobulinemia. After an 18-month follow-up, renal function remained stable with serum creatinine at 107  $\mu\text{mol/L}$ .

Waldenström's disease is a non-Hodgkin lymphoma with mature B cells characterized by medullary lymphoplasmacytic infiltration and secretion of a monoclonal immunoglobulin (IgM). It is a very rare malignant hemopathy, with an average age at diagnosis of 63 years [29]. In monoclonal cryoglobulinemia related to Waldenström disease, the use of TA, combined with chemotherapy, is most often indicated in cases of symptomatic hyper-viscosity syndrome. Indeed, Schwab and Fahey were the first to describe the effectiveness of plasma exchange to reduce plasma viscosity with reversibility of the associated clinical manifestations (retinopathy and heart failure) in two patients followed for Waldenström disease [7, 30].

There is indeed a relationship between the level of circulating IgM and plasma viscosity. A single plasmapheresis session of about 3 L allows regression of plasma viscosity by more than 50%. TA has now become established as an emergency treatment for hyper-viscosity syndromes by demonstrating its effectiveness in the rapid control of clinical manifestations (ocular, neurological, etc.). It should be started urgently as soon as clinical signs appear, or prophylactically in conjunction with the initiation of drug treatments, in particular with rituximab [29, 31–36]. TA can also be used long term to maintain normal plasma viscosity in patients who are intolerant or refractory to chemotherapy [35]. Renal involvement during cryoglobulinemia (which may be type I or II) linked to Waldenström disease or monoclonal proliferation of the IgM type is rare. It is the glomerular type in the majority of cases, but this generally has a poor prognosis and most often progresses to needing dialysis. Thus, this could

justify the use of TA to allow rapid reduction of IgM and serum cryoglobulin levels to reduce renal damage, as we observed in our series of patients (Table 1). The timing of apheresis sessions was essentially guided by the kinetics of IgM and the evolution of nephrotic syndrome.

Bezzi et al. [37] reported on the case of a 39-year-old subject who presented with glomerular-type kidney damage secondary to type I cryoglobulinemia in Waldenström disease. He received chemotherapy and seven plasma exchanges with spectacular results after the third PE (normalization of blood pressure and negative cryoglobulinemia, stable renal function, with a eGFR of 40 ml/min/1.73 m<sup>2</sup>, proteinuria of 2.1 g/day). However, when plasma exchange was stopped, there was reappearance of cryoglobulinemia, which required the resumption of treatment.

Skin ulcers secondary to cryoglobulinemia can pose a therapeutic challenge. The addition of apheresis sessions to immunosuppressive therapy can be considered for non-healing and recurrent refractory ulcers. Several cases have been reported in the literature [22, 38, 39] showing the effectiveness of apheresis, particularly plasma exchanges, in improving skin lesions secondary to cryoglobulinemia.

In our series, the patient that presented with recurrent foot ulcers associated with type I cryoglobulinemia secondary to monoclonal IgM kappa gammopathy was initially treated with rituximab alone (annual infusion at a dose of 375 mg/m<sup>2</sup>). The addition of DFPP sessions (10 sessions at three sessions per week for 2 weeks, then two sessions per week for 2 weeks) enabled, on the 8th day of treatment, a marked improvement in pain and the ulcers beginning to heal. No signs of vasculitis activity were reported at 16 months follow-up (no recurrence of skin ulcers, negative cryoglobulinemia).

## 5 | CONCLUSIONS

Treatment with therapeutic apheresis (DFPP or PE) for patients with cryoglobulinemic vasculitis is used in cases of severe and/or refractory renal, cutaneous, digestive, cardiac, or neurological involvement. It seems to be important to offer TA at the beginning to achieve a faster and sustained clinical-biological response, with its duration determined according to the clinical evolution and its frequency guided by the biological parameters (IgM, cryoglobulin, proteinuria, etc.). However, a prospective multicenter randomized study is essential to confirm our hypothesis.

## AUTHOR CONTRIBUTIONS

Augustin Twite Banza collected the data; Hamza Naciri Bennani wrote the manuscript that was edited by Lionel

Rostaing, Johan Noble, and Thomas Jouve; Florian Terrec, Hamza Naciri Bennani, Lionel Motte, and Paolo Malvezzi supervised the DFPP sessions. Lionel Rostaing conceptualized the study.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

All data are available upon request to the corresponding author.

## ETHICS STATEMENT

The study was conducted according to the guidelines of the Declaration of Helsinki. Ethical review and approval were waived for this study because data collection was approved by CNIL (French National committee for data protection; approval number 1987785v0).

## ORCID

Lionel Rostaing  <https://orcid.org/0000-0002-5130-7286>

## REFERENCES

1. Brouet JC, Clauvel JP, Danon F, Klein M, Seligmann M. Biologic and clinical significance of cryoglobulins. A report of 86 cases. *Am J Med.* 1974;57(5):775–88. [https://doi.org/10.1016/0002-9343\(74\)90852-3](https://doi.org/10.1016/0002-9343(74)90852-3)
2. Karras A. Renal involvement of cryoglobulinemia. *Nephrol Ther.* 2018;14(2):118–26. <https://doi.org/10.1016/j.nephro.2018.02.003>
3. Wintrobe MM, Buell MV. Hyperproteinemia associated with multiple myeloma. With report of a case in which an extraordinary hyperproteinemia was associated with thrombosis of the retinal veins and symptoms suggesting Raynaud's disease. *Bull John Hopkins Hosp.* 1933;52:156.
4. Lerner AB, Watson CJ. Studies of cryoglobulins; unusual purpura associated with the presence of a high concentration of cryoglobulin (cold precipitable serum globulin). *Am J Med Sci.* 1947;214(4):410–5. <https://doi.org/10.1097/00000441-194710000-00009>
5. Kuo G, Choo QL, Alter HJ, Gitnick GL, Redeker AG, Purcell RH, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science.* 1989; 244(4902):362–4. <https://doi.org/10.1126/science.2496467>
6. Gulli F, Santini SA, Napodano C, Bottoni P, Pocino K, Rapaccini GL, et al. Cryoglobulin test and cryoglobulinemia hepatitis C-virus related. *Mediterr J Hematol Infect Dis.* 2017; 9(1):e2017007. <https://doi.org/10.4084/MJHID.2017.007>
7. Schwab PJ, Fahey JL. Treatment of Waldenström's macroglobulinemia by plasmapheresis. *N Engl J Med.* 1960;263:574–9. <https://doi.org/10.1056/NEJM19600922631202>
8. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice: evidence-based approach from the writing Committee of the American Society for apheresis—the eighth special issue. *J Clin Apher.* 2019;34(3):171–354. <https://doi.org/10.1002/jca.21705>

9. Kaplan AA. Therapeutic plasma exchange: a technical and operational review. *J Clin Apher.* 2013;28(1):3–10. <https://doi.org/10.1002/jca.21257>
10. Okuyama H, Kimura S, Fujimoto K, Imura J, Chikazawa Y, Nakagawa M, et al. A case of chronic hepatitis C with nephrotic diabetic nephropathy who achieved sustained viral remission by double-filtration plasmapheresis and interferon combination therapy. *Intern Med.* 2012;51(15):1991–5. <https://doi.org/10.2169/internalmedicine.51.7117>
11. Muro K, Toda N, Yamamoto S, Yanagita M. The successful treatment of a case of HCV-associated cryoglobulinemic glomerulonephritis with rituximab, direct-acting antiviral agents, plasmapheresis and long-term steroid despite serologically persistent cryoglobulinemia. *Intern Med.* 2021;60(4):583–9. <https://doi.org/10.2169/internalmedicine.5461-20>
12. Taniyama Y, Nakatani Y, Matsuoka T, Takahashi M, Shimizu K, Yamamoto S, et al. Efficacy of cryofiltration for treatment of mixed cryoglobulinemia: a report of four cases. *Ther Apher Dial.* 2017;21(3):238–42. <https://doi.org/10.1111/1744-9987.12556>
13. Siami GA, Siami FS. Intensive tandem cryofiltration apheresis and hemodialysis to treat a patient with severe calciphylaxis, cryoglobulinemia, and end-stage renal disease. *ASAIO J.* 1999;45(3):229–33. <https://doi.org/10.1097/00002480-199905000-00024>
14. Ferri C, Moriconi L, Gremignai G, Migliorini P, Paleologo G, Fosella PV, et al. Treatment of the renal involvement in mixed cryoglobulinemia with prolonged plasma exchange. *Nephron.* 1986;43(4):246–53. <https://doi.org/10.1159/000183849>
15. Reik L Jr, Korn JH. Cryoglobulinemia with encephalopathy: successful treatment by plasma exchange. *Ann Neurol.* 1981;10(5):488–90. <https://doi.org/10.1002/ana.410100514>
16. Kiyomoto H, Hitomi H, Hosotani Y, Hashimoto M, Uchida K, Kurokouchi K, et al. The effect of combination therapy with interferon and cryofiltration on mesangial proliferative glomerulonephritis originating from mixed cryoglobulinemia in chronic hepatitis C virus infection. *Ther Apher.* 1999;3(4):329–33. <https://doi.org/10.1046/j.1526-0968.1999.00196.x>
17. Sinha D, Lambie M, Krishnan N, McSorley K, Hamer R, Lowe D, et al. Cryofiltration in the treatment of cryoglobulinemia and HLA antibody-incompatible transplantation. *Ther Apher Dial.* 2012;16(1):91–6. <https://doi.org/10.1111/j.1744-9987.2011.01004.x>
18. Marson P, Monti G, Montani F, Riva A, Mascia MT, Castelnovo L, et al. Apheresis treatment of cryoglobulinemic vasculitis: a multi-centre cohort study of 159 patients. *Transfus Apher Sci.* 2018;57(5):639–45. <https://doi.org/10.1016/j.transci.2018.06.005>
19. Yang CH, Qureshi AA, Churchill WH, Saavedra AP. Long-term plasmapheresis in conjunction with thalidomide and dexamethasone for the treatment of cutaneous ulcers and neovascular glaucoma in recalcitrant type I cryoglobulinemia. *JAMA Dermatol.* 2014;150(4):426–8. <https://doi.org/10.1001/jamadermatol.2013.8700>
20. Ramunni A, Lauletta G, Brescia P, Salianni MT, Montrone M, Chironna M, et al. Double-filtration plasmapheresis in the treatment of leg ulcers in cryoglobulinemia. *J Clin Apher.* 2008;23(3):118–22. <https://doi.org/10.1002/jca.20166>
21. Stefanutti C, Vivencio A, di Giacomo S, Labbadia G, Mazza F, D'Alessandri G, et al. Immunoabsorption apheresis and immunosuppressive drug therapy in the treatment of complicated HCV-related cryoglobulinemia. *J Clin Apher.* 2009;24(6):241–6. <https://doi.org/10.1002/jca.20222>
22. Olson N, Yerrabothala S, Dunbar N. Successful use of cryocrit for monitoring response to therapeutic plasma exchange in type 1 cryoglobulinemia. *J Clin Apher.* 2016;31(4):403–4. <https://doi.org/10.1002/jca.21414>
23. Delaney VB, Fraley DS, Segal DP, Bruns FJ. Plasmapheresis as sole therapy in a patient with essential mixed cryoglobulinemia. *Am J Kidney Dis.* 1984;4(1):75–7. [https://doi.org/10.1016/s0272-6386\(84\)80031-1](https://doi.org/10.1016/s0272-6386(84)80031-1)
24. Braun A, Neumann T, Oelzner P, Hein G, Gröne HJ, Ziemer M, et al. Cryoglobulinaemia type III with severe neuropathy and immune complex glomerulonephritis: remission after plasmapheresis and rituximab. *Rheumatol Int.* 2008;28(5):503–6. <https://doi.org/10.1007/s00296-007-0462-y>
25. Stefanutti C, di Giacomo S, Mareri M, De Lorenzo F, D'Alessandri G, Angelico F, et al. Immunoabsorption apheresis (Selesorb) in the treatment of chronic hepatitis C virus-related type 2 mixed cryoglobulinemia. *Transfus Apher Sci.* 2003;28(3):207–14. [https://doi.org/10.1016/s1473-0502\(03\)00055-7](https://doi.org/10.1016/s1473-0502(03)00055-7)
26. Scarpato S, Tirri E, Naclerio C, Moscato P, Salvati G. Plasmapheresis in cryoglobulinemic neuropathy: a clinical study. *Dig Liver Dis.* 2007;39(supl 1):S136–7. [https://doi.org/10.1016/s1590-8658\(07\)80027-2](https://doi.org/10.1016/s1590-8658(07)80027-2)
27. Namba T, Shiba R, Yamamoto T, Hirai Y, Moriwaki T, Matsuda J, et al. Successful treatment of HCV-related cryoglobulinemic glomerulonephritis with double-filtration plasmapheresis and interferon combination therapy. *Clin Exp Nephrol.* 2010;14(4):372–6. <https://doi.org/10.1007/s10157-010-0282-3>
28. Comarmond C, Cacoub P, Saadoun D. Treatment of chronic hepatitis C-associated cryoglobulinemia vasculitis at the era of direct-acting antivirals. *Therap Adv Gastroenterol.* 2020;13:1756284820942617. <https://doi.org/10.1177/1756284820942617>
29. Stone MJ. Waldenström's macroglobulinemia: hyperviscosity syndrome and cryoglobulinemia. *Clin Lymphoma Myeloma.* 2009;9(1):97–9. <https://doi.org/10.3816/CLM.2009.n.026>
30. Solomon A, Fahey JL. Plasmapheresis therapy in macroglobulinemia. *Ann Intern Med.* 1963;58:789–800. <https://doi.org/10.7326/0003-4819-58-5-789>
31. Menke MN, Feke GT, McMeel JW, Treon SP. Ophthalmologic techniques to assess the severity of hyperviscosity syndrome and the effect of plasmapheresis in patients with Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma.* 2009;9(1):100–3. <https://doi.org/10.3816/CLM.2009.n.027>
32. Zarkovic M, Kwaan HC. Correction of hyperviscosity by apheresis. *Semin Thromb Hemost.* 2003;29(5):535–42. <https://doi.org/10.1055/s-2003-44560>
33. Treon SP. How I treat Waldenström macroglobulinemia. *Blood.* 2009;114(23):2375–85. <https://doi.org/10.1182/blood.2019000725>
34. Vijay A, Gertz MA. Waldenström macroglobulinemia. *Blood.* 2007;109(12):5096–103. <https://doi.org/10.1182/blood-2006-11-055012> Epub 2007 Feb 15.
35. Johnson SA, Birchall J, Luckie C, Oscier DG, Owen RG. Haemato-oncology task force of the British Committee for Standards in haematology: guidelines on the management of



- Waldenström macroglobulinaemia. *Br J Haematol*. 2006; 132(6):683–97. <https://doi.org/10.1111/j.1365-2141.2005.05948.x>
36. Stone MJ, Bogen SA. Evidence-based focused review of management of hyperviscosity syndrome. *Blood*. 2012;119(10): 2205–8. <https://doi.org/10.1182/blood-2011-04-347690>
37. Bezzi L, Saad Djaballah D, Benkacimi N, Benrabah K, Kastali M, Shelghoum S, et al. Atteinte rénale au cours de la maladie de Waldenstrom avec cryoglobulinémie chez un sujet jeune: à propos d'un cas. *Nephrol Ther*. 2019;15(5):372.
38. Vila AT, Barnadas MA, Ballarin J, Garcia R, Juarez C, Madoz P, et al. Cutaneous ulcers with type I cryoglobulinemia treated with plasmapheresis. *Eur J Dermatol*. 2004;14(3):186–9.
39. Tallarita T, Gagliano M, Corona D, Giuffrida G, Giaquinta A, Zerbo D, et al. Successful combination of rituximab and plasma

exchange in the treatment of cryoglobulinemic vasculitis with skin ulcers: a case report. *Cases J*. 2009;2:7859. <https://doi.org/10.4076/1757-1626-2-7859>

**How to cite this article:** Naciri Bennani H, Banza AT, Terrec F, Noble J, Jouve T, Motte L, et al. Cryoglobulinemia and double-filtration plasmapheresis: Personal experience and literature review. *Ther Apher Dial*. 2023;27(1):159–69. <https://doi.org/10.1111/1744-9987.13885>